II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-4, 7-23, 25, 32-43, and 69-78 were pending and under examination at the time of the Office Action dated August 29, 2006. Claims 1-2, 4, 36, 69, and 78 have been amended. Claims 3 and 74 have been canceled. Claim 2 has been withdrawn as being directed to a non-elected invention. Thus, claims 1, 4, 7-19, 20-23, 25, 32-43, 69-73, and 75-78 are currently under examination. Support for the amendments to claims 1-2, 4, and 78 can be found in the specification at, for example, page 8, ln. 12-25. Support for the amendment to claim 36 can be found in the specification at, for example, page 23, ln. 16-29; page 27, ln. 2-11; page 34, ln. 21-25. Claim 69 has been amended to depend from claim 32 rather than from canceled claim 68. No new matter was added by these amendments.

B. Amendments to the Specification

Applicants request that Elizabeth Grimm be deleted as an inventor pursuant to 37 C.F.R. § 1.48(b), because the cancellation of claims during the prosecution of the present application has resulted in this person's invention no longer being claimed. The processing fee set forth in 37 C.F.R. § 1.17(i) is provided.

C. Claims 1-4, 7-25, 32-43, and 68-77 Are Enabled

The Action rejects claims 1-4, 7-23, 25, 32-43, and 69-78 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Although the Action admits the specification is enabling for intratumoral injection of a nucleic acid expressing full-length or secreted MDA-7, it is alleged that the specification does not reasonably provide enablement for distal or systemic administration of an adenoviral vector expressing any fragment of MDA-7 polypeptides for treating an angiogenesis-dependent tumor. Action at page 3-4. This Action also indicates that the

reasoning previously provided for this rejection in prior Actions still applies. Applicants respectfully traverse this rejection.

1. Routes of Administration

This Action and previous Actions raised several issues regarding routes of administration that indicate undue experimentation would be required to practice the invention. These related to gene therapy and viral vectors. Applicants respectfully traverse this ground of the rejection.

a) Gene Therapy

The Action contends that the gene therapy practitioner recognized that gene therapy for angiogenesis and cancer was neither accepted nor routine and that such a person awaited significant development and guidance for its practice. The Action relies on the references of Deonarain, Miller, Makrides *et al.* ("Makrides"), and Boucher *et al.* ("Boucher") for its position that gene targeting to desired cells and tissue has yet to become routine in the art. Deonarain is said to illustrate this point.

Moreover, the Action contends that Miller illustrates that no single vector is considered to be universally appropriate. Miller is alleged to teach that because of the underdeveloped state of vector targeting, that gene therapy, as represented by the cystic fibrosis treatment, has relied largely on localized delivery.

Furthermore, the Makrides reference was cited to provide further evidence that there is an association between the vector system chosen and the production of a therapeutic protein, which is relevant to therapeutic efficacy. The Boucher reference is cited as indicating that another element critical to the success of gene delivery is the host resistance to foreign gene transfer. It is said to be relevant because it says that host cells have an innate ability to defend themselves against the penetration of gene therapy vectors.

Once again, a closer examination of the cited references reveals that they do not support the Action's conclusions and also, there is evidence that indicates gene therapy can be practiced according to the specification and knowledge of the skilled artisan.

The Action cites the reference of Miller as saying, "No single delivery system is likely to be universally appropriate, for instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer." Action dated 6/15/04 at page 8, citing page 190 of Miller. By its own admission, the Action renders the next citation to Miller and the citation to Boucher irrelevant because they both involve statements relating to the treatment of cystic fibrosis, while the present invention is related to inhibiting angiogenesis.

As for the reliance on the reference of Makrides, this reference merely states that "the choice of an expression system for production of recombinant proteins depends on many factors...." However, it is not clear how this statement indicates that undue experimentation would be required to practice the invention. Moreover, this reference says nothing about the ability to express MDA-7 or any limitations there might be with its expression.

It is well settled that in examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of 35 U.S.C. § 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, (CCPA. 1971). The Examiner must supply a factual basis or scientific principle to reasonably doubt the accuracy of a clear disclosure. *In re Marzocchi*, 439 F.2d at 224. The Examiner's reliance on Miller, Boucher, and Makrides, however, fails to provide a factual basis or scientific principle to reasonably doubt the accuracy of the present disclosure.

In fact, the weight of the evidence supports the conclusion that the claims are enabled. In addition to the data regarding a therapeutic effect from administration of Ad-mda7 in the

specification (Examples 1, 4, 6, 9, 10 and 11), there is information relating to the administration of an MDA-7-encoding plasmid in a DOTAP:cholesterol liposome to a nude mouse. In the Declaration of Sunil Chada ("2003 Chada Declaration"), Dr. Chada sets forth that nude mice with tumors exhibited reduced tumor growth and reduced levels of CD31 staining after treatment with the DOTAP:Chol-*mda-7* complex. Declaration at ¶ 9. A reduction in levels of CD31 staining is indicative of reduced vascularization, *i.e.,* inhibition of angiogenesis.

Additionally, other evidence indicates the invention will work even if the MDA-7 is not administered intratumorally. As described in the specification, cells that take up the construct and express the therapeutic polypeptide encoded by the nucleic acid can secrete the protein which may interact with neighboring cells not transduced or infected by an expression construct (Specification, p. 27, ln. 3-12). Example 3 in the present specification demonstrates that secreted MDA-7 protein induces killing in cancer cells. Furthermore, in a published patent application with some of the same inventors, there is additional data regarding MDA-7 and angiogenesis. In WO 04/078124, it states in Example 7:

> Studies were conducted to determine whether sMDA-7 produced by 293-mda-7 cells can systemically inhibit tumor growth. Mice were inoculated subcutaneously with A549 tumor cells in the lower right flank. When the tumors reached 50-100 mm^3, 293 cells producing sMDA-7 protein (293-mda-7 cells) or parental 293 cells (control) were encapsulated in Matrigel and implanted subcutaneously in the upper right flank. Tumor measurement was initiated after implantation of 293 cells. The growth of A549 lung tumor xenografts was significantly less ($P = 0.001$) in the mice treated with 293-mda-7 cells than in the control group (FIG. 6D). Compared with tumor growth in the control mice, the growth of the tumors in mice implanted with the encapsulated 293-mda-7 cells was suppressed by 40-50%. To confirm that the inhibitory effect was due to sMDA-7, serum samples from animals were tested for MDA-7 protein by western blot analysis and ELISA. Intense banding of sMDA-7 at the expected 40-kDa size was observed in the serum of animals implanted with 293-mda-7 cells by western blot analysis. However, faint bands were also observed in the serum of control animals, indicating some cross-reactivity with mouse serum proteins. The serum levels of circulating sMDA-7 detected by ELISA 3 days postimplantation was approximately 50 ng/ml.

> At the end of the experiment, tumors and injected Matrigel containing 293-mda-7 cells were harvested and evaluated. Gross examination of the tumors indicated that the tumor growth in animals that received 293-mda-7 cells was inhibited. Histopathologic analysis of the tumor tissues demonstrated no differences between the specimens from animals receiving 293 cells and those from animals receiving 293-mda-7 cells. Additionally, the tumors from mice treated with 293-mda-7 were significantly ($P = 0.001$) less vascular than were the tumors from mice treated with parental 293 cells, as evidenced by CD31-positive staining (FIG. 6E). Immunohistochemical analysis of the Matrigel from animals receiving 293-mda-7 cells demonstrated MDA-7 protein expression. In contrast, MDA-7 was not detected in the Matrigel recovered from animals receiving parental 293 cells. These results demonstrate that **sMDA-7 systemically** inhibited tumor growth **by inhibiting angiogenesis**.

WO 04/078124 at page 122 (emphasis added). This text indicates that subcutaneous administration of MDA-7 in the upper flank—as opposed to the lower flank where the tumor was—achieved systemic inhibition of angiogenesis. Post-filing date successes following the *teachings* of the application at issue are probative to show enablement of the claimed invention. *See Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987) (stating that a later dated publication ... [may be] offered ... as evidence that the disclosed device would have been operative). This additional evidence indicates the claimed invention is enabled beyond just intratumoral injection.

The Action notes that Example 7 in WO 04/078124 describes implanting encapsulated and transfected 293 cells for *in vivo* MDA-7 delivery, and that the example does not teach administering a nucleic acid systemically wherein a nucleic acid reaches target cells at a remote site. While Example 7 in WO 04/078124 may not disclose the systemic delivery of a nucleic acid, it does demonstrate that mda-7 transfected cells at a site remote from the target tumor can inhibit the growth of the target tumor by inhibiting angiogenesis. This supports the claimed invention by demonstrating that cells at the tumor site need not be directly transfected with an mda-7 encoding nucleic acid, but can be treated by MDA-7 protein secreted from transfected

cells at a distal site. This is also consistent with the teachings in the present specification, such as in Example 3 where it was shown that secreted MDA-7 protein induces killing in cancer cells.

b) Viral Vectors

The Action contends that adenovirus tissue tropism in respiratory epithelium cells offers additional evidence that targeting of adenovirus may be required for gene therapy. It states that the reference of Miller teaches that adenoviral diseases are usually associated with respiratory epithelium. It contends that the issue of tissue tropism has been raised because if viral vectors are administered systemically from a site distal from a tumor, it may require a targeting mechanism so that a sufficient amount of the vector can be localized to the site of the targeted tumor.

Applicants note that this is arguably relevant to only one particular embodiment of the claimed invention: systemic delivery of an adenovirus vector to non-lung tissue. The specification indicates that different routes of administration are contemplated depending on the location and nature of the lesion. Specification at page 54, lines 25-30. The specification indicates that for treatment of a tumor, administration intratumorally is specifically contemplated but that continuous administration may be applied when appropriate, for example, to a tumor bed. Specification at pages 55-56. This shows two things. First, the specification teaches a situation in which systemic administration can be accomplished without tissue tropism being an issue. Second, it shows that the skilled artisan was aware that different situations call for different considerations in terms of mode of administration and construct used.

Moreover, Applicants address the issue of whether adenovirus can infect other tissues. The specification of the instant application shows that adenovirus infected breast cancer cells (Example 4), in addition to lung cancer cells (Example 10). Moreover, numerous publications

and patent applications have shown that adenovirus[1] can be used to treat a multitude of different cancers and infect a wide variety of tissues in animals and patients; these include, for example, bladder (Pagliaro *et al.*), breast (WO 04/078124 page 190-191), glioma (Lang *et al.*), head and neck (Clayman *et al.*), prostate (Pisters *et al.*), and ovarian (Wolf *et al.*).

Applicants submit that the tropism issue raised in the Action does not render the claimed invention not enabled. Consequently, they respectfully request this rejection be withdrawn.

D. Claims 75 and 76 Are Definite

The Action rejects claims 75 and 76 as indefinite because it contends that claims 75 and 76 use the term "viral particles" and that this term lacks antecedent basis in claim 8, which recites "viral vector." It cites a Google definition as evidence. Applicants respectfully traverse this rejection.

A proper evaluation of claims 75 and 76 under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification as interpreted by one of ordinary skill in the art. Moreover, use of well-known terms of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983). Claims may, therefore, make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *Id.*

Amounts of viral vectors are conventionally given in "viral particles" or "plaque-forming units." Viral particle counts are typically measured using an electron microscope, whereas plaque-forming units (*i.e.,* pfu) are measured using an infectivity titer. These terms are well known to those in the art. The specification confirms this. It states, "In certain embodiments, the

[1] Applicants cite publications involving Advexin®, an adenovirus product carrying the p53 gene, which is owned by Introgen Therapeutics, Inc., the licensee of the present application.

nucleic acid is a viral vector, wherein the viral vector dose is or is at least 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13} or higher pfu or viral particles." Specification at page 9, lines 15-17. Moreover, the "Google" definitions cited in the Action do not contradict this understanding. The term "viral vector" is said to mean "a type of virus used in cancer therapy." The term "viral particles" refers to "the new viruses reproduced inside a cell." Both terms refer to viruses.

Claim 8 specifies that the expression vector is a viral vector. Claim 75, which depends from claim 8, specifies the amount of viral vector in "viral particles." Claim 76 depends from claim 75 and further defines the amount of viral vector in "viral particles." Thus, claims 75 and 76 specify the amount of viral vector in units of measure well-known to those in the art.

In view of the above, the skilled artisan would understand that the number of viral particles referred to in claims 75 and 76 refers to the amount of viral vector. The term "viral particles" is, therefore, definite, and claims 75 and 76 satisfy all of the requirements under 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request this rejection be withdrawn.

E. Claims 1-4, 7, 8, 10-15, 24, 25, 32-36, 42, 43, 68-74, and 77 Are Not Anticipated or Obvious

The Action rejects claims 1-4, 7, 8, 10-15, 25, 32-36, 42, 43, 69-74, 77, and 78 under 35 U.S.C. § 102(e) as anticipated by or in the alternative under 35 U.S.C. § 103(a) as obvious over Fisher *et al.* (U.S. Patent 6,355,622) ("Fisher"), as evidenced by Folkman *et al.*, *Nature*, 339:58-61, 1989 and *J. Biol. Chem.*, 267:10931, 1992 ("Folkman references"). Fisher is said to teach a method of inhibiting cancer in a subject comprising intratumoral administration to nude mice bearing cervical carcinoma cells replication deficient adenoviral vector encoding full-length mda-7 protein. The Action admits that Fisher does not literally teach that a tumor is an angiogenesis-related disease. The Action argues, however, that it was well known in the art that

tumors belong to the class of angiogenesis-related diseases and that angiogenesis accompanies tumor growth and metastasis as evidenced by the Folkman references. The Action concludes that Fisher meets every limitation of the elected species, and thus, anticipates the claimed invention. Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Current claim 1 recites:

> A method of inhibiting angiogenesis in a human patient, wherein the patient has an angiogenesis-dependent cancer or an angiogenesis-related disease other than cancer, comprising administering to the patient an effective amount of a human melanoma differentiation antigen-7 (MDA-7) polypeptide or a nucleic acid expressing the human MDA-7 polypeptide in eukaryotic cells to inhibit angiogenesis in the angiogenesis-dependent cancer or the angiogenesis-related disease other than cancer.

The Fisher patent does not mention angiogenesis, much less teach a method of inhibiting angiogenesis in a patient having an angiogenesis-dependent cancer. In fact, the Action concedes that Fisher does not teach a method of inhibiting angiogenesis (Action, p. 10). Nevertheless, the Action argues that because the Folkman reference teaches that cancer is "an angiogenesis-related disease," this is evidence that Fisher inherently teaches every element of the claimed invention. This argument is insufficient to establish a *prima facie* case of anticipation.

As noted by Vermeulen *et al.*, there are increasing numbers of exceptions to the "Folkman-hypothesis" that solid tumors need angiogenesis to grow (*Histopathology*, 40:105-107 (2002)). For example, Maniotis *et al.* reported what was termed "vasculogenic mimicry" in human melanoma cells *in vivo* and *in vitro* by which aggressive melanoma cells generated vascular channels that facilitated tumor perfusion independent of tumor angiogenesis (*Am. J. Pathol.*, 155:739-752 (1999)). Pezzella *et al.* reported that in 16% of primary stage I non-small-cell lung carcinomas examined, the tumor was able to exploit an existing vascular bed and grow

without inducing angiogenesis (*Am. J. Pathol.*, 151:1417-1423 (1997)). More recently, Sakariassen *et al.* described studies of glioblastoma cells xenografted in the brains of rats and reported that the implanted tumor spheroids developed tumors with a stem-like, nonangiogenic and highly invasive phenotype (*Proc. Nat'l. Acad. Sci.*, 103:16466-16471 (2006)). Accordingly, not all cancers are angiogenesis-dependent cancers, and the present Action fails to establish that Fisher teaches an angiogenesis-dependent cancer.

With regard to the Action's argument that Fisher inherently discloses the claimed invention, Applicants note that "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002). Furthermore, it is the Examiner's burden to provide a rationale or evidence to show inherency. MPEP § 2112(IV). In the present rejection, the Action asserts that cancer is "an angiogenesis-related disease, and angiogenesis accompanies tumor growth and metastasis as evidenced by Folkman *et al.*" As described above, however, not all cancers are necessarily angiogenesis-dependent cancers. A method of treating cancer, therefore, is not necessarily a method of treating an angiogenesis-dependent cancer nor is it necessarily a method of inhibiting angiogenesis.

Inherent anticipation cannot be based on probabilities or possibilities. In *MEHL/Biophile Int'l Corp. v. Milgraum,* the CAFC held that a claim that included the step of aligning a laser light applicator substantially vertically over a hair follicle opening was not inherently anticipated by a manual that taught aiming the laser at skin pigmented with tattoo ink because an operator of the laser could use the laser according to the manual without necessarily aligning the laser substantially vertically over a hair follicle opening. 192 F.3d 1362, 1365 (Fed. Cir. 1999). In *Perricone v. Medicis Pharmaceutical Corp.*, the CAFC held that claims directed to a method for

treating skin sunburn by topically applying to the skin sunburn a fatty acid ester of ascorbic acid were not inherently anticipated by a reference that disclosed topically applying the same composition to skin but not to skin sunburn. 432 F.3d 1368, 1379 (Fed. Cir. 2005).

Furthermore, Fisher does not "intrinsically" or inherently anticipate the claimed invention because Fisher's method was effected in mice, not humans. Anticipation requires that ***every*** element be taught. Fisher never performed the method in humans and, and therefore, Fisher does not inherently or "intrinsically" anticipate the claimed invention.

The Action also fails to establish a *prima facie* case of anticipation in regard to claim 36 and the claims that depend from it because the Action does not allege, much less establish, that Fisher discloses a method of inhibiting endothelial cell differentiation in a human patient having a disease of excessive or abnormal stimulation of endothelial cells comprising administering to the endothelial cells of the patient an effective amount of an MDA-7 polypeptide or a nucleic acid molecule expressing the human MDA-7 polypeptide.

For at least the reasons above, the present Action fails to establish a *prima facie* case of anticipation because the Action does not establish that Fisher necessarily discloses a method of inhibiting angiogenesis in a human patient, wherein the patient has an angiogenesis-dependent cancer. Moreover, the Action does not even allege that Fisher discloses a method of inhibiting endothelial cell differentiation as recited in claims 36-43. Applicants, therefore, request the withdrawal of this rejection.

Furthermore, the claimed invention was not obvious in view of Fisher because the results were surprising and unexpected. Significantly, no mention is made of angiogenesis in the Fisher reference. The focus on MDA-7 as only an apoptosis inducer is in distinct contrast to the instant application, which is why it was surprising and unexpected that MDA-7 could inhibit

angiogenesis. The present specification provides specific data that the process of angiogenesis is specifically inhibited. On page 92 at lines 15-20 the specification indicates that tumors treated *in vivo* with Ad-mda7 had fewer blood vessels than untreated tumors. Furthermore, on page 99, data is provided that tumors treated with Ad-mda7 had significantly lower levels of CD31 expression, which indicates fewer blood vessels. The application also showed that MDA-7 inhibited endothelial cell differentiation *in vitro* (page 98) and inhibited tube formation (page 100). Therefore, Fisher neither anticipates or renders obvious the claimed invention. Accordingly, Applicants respectfully request this rejection be withdrawn.

F. Claims 1-4, 7-25, 35-43, and 68-77 Are Provisionally Rejected

The Action provisionally rejects claims 1-4, 7-23, 25, 35-43, and 69-78 under 35 U.S.C. § 102(e) over copending Application No. 09/615,154. It states that if this application were to publish under 35 U.S.C. § 122(b) or be patented, the rejection would no longer be provisional.

Because the rejection is provisional, Applicants need not address this rejection at this time.

G. Claims 1-4, 7-25, 35-43, and 68-77 Are Not Derived from a Co-Pending Application

The Action rejects claims 1-4, 7-23, 25, 35-43, and 69-78 under 35 U.S.C. § 102(f) over copending Application No. 09/615,154. The Action argues that because the elected invention is drawn to treating an angiogenesis-related tumor in a patient, the instant claims are anticipated by the co-pending application. Applicants respectfully traverse this rejection.

As evidenced by the attached declaration of Sunil Chada, Rajagopal Ramesh, and Abner Mhashilkar under 37 C.F.R. § 1.132, the study of angiogenesis described in Application No. 09/615,154 is a description of the Applicants' own work. Dr. Ramesh approves of the declaration, but was unable to return his signed declaration to Applicants' representative prior to

the filing of this response. Dr. Ramesh's signed declaration will be submitted to the Patent and Trademark Office as soon as it is available.

The declaration of Sunil Chada, Rajagopal Ramesh, and Abner Mhashilkar overcomes the section 102(f) rejection based on Application No. 09/615,154. *See* MPEP § 2137. Applicants, therefore, respectfully request this rejection be withdrawn.

H. Claims 1, 7-9, 16-23, 36-41, 75, and 76 Are Not Obvious over Roth and Fisher

The Action rejects claims 1, 7-9, 16-23, 36-41, 75, and 76 under 35 U.S.C. § 103(a) as being unpatentable over Fisher (U.S. Patent 6,355,622) in view of Roth *et al.* (U.S. Patent 6,069,134) ("Roth"), and as evidenced by Nasz *et al.* (Acta Microbiol Immunol Hung 48:323-48 (2001)). Applicants respectfully traverse this rejection.

The invention is directed to a method of inhibiting angiogenesis. The cited references simply do not teach this. A proper *prima facie* case of obviousness requires that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP §2142. Furthermore, obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Roth, Fisher, and Nasz do not disclose a method of inhibiting angiogenesis. Furthermore, as discussed above in regard to the Fisher reference, not all cancers are angiogenesis-dependent cancers. Thus, a method of treating cancer is not necessarily a method of treating an angiogenesis-dependent cancer nor is it necessarily a method of inhibiting angiogenesis. Consequently, Fisher, Roth, and Nasz do not teach or suggest all of the claim limitations. Accordingly, a proper *prima facie* case has not been made.

Notwithstanding the absence of a proper ground for rejections, Applicants further provide evidence discussed above that that the claimed invention was surprising and unexpected. A role for MDA-7 in cancer was provided solely in the context of terminal differentiation and

apoptosis. Its effect in cancer was concentrated only on cancer cells; there was no suggestion or teaching that it may have an effect on angiogenesis, much less the ability to actually *inhibit angiogenesis*. *See* Su *et al.* and Fisher. The present rejection cites to Roth, which involves a different tumor suppressor gene. In Roth, p53 is discussed only in the context of apoptosis as well. *See e.g.,* first paragraph of Summary of Invention. Therefore, it was surprising and unexpected that MDA-7 could inhibit angiogenesis, particularly by reducing the amount of CD31 expressed—which is indicative of fewer blood vessels in tumors—and by reducing tube formation in HUVEC cells.

Moreover, it was surprising and unexpected that the human MDA-7 protein would act on the non-human cells in the *in vivo* mouse model. Neither Fisher nor Roth provides any indication that this would be the case.

Therefore, there are several grounds for the nonobviousness of the claimed invention. Applicants respectfully request this rejection be withdrawn.

I. Double Patenting Rejection Is Provisional

Claims 1-4, 7-23, 25, 32, 35-43, 69-74, 77, and 78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 92-116, 125-154, and 159-174 of copending U.S. Patent Application 09/615,154 ('154 application). The Action also provisionally rejects claims 1-4, 7-23, 25, 32, 35-43, 69-74, 77, and 78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 70-74 of Application No. 10/378,590, and claims 38-41 of Application No. 11/156,521. Applicants traverse these rejections.

A method of inhibiting angiogenesis is not a species of a method of treating cancer, even if the method of inhibiting angiogenesis is in a patient with an angiogenesis-related cancer because not all cancer treatments will achieve inhibition of angiogenesis and not all cancers are

agniogenesis-dependent cancers. Moreover, the current claim in the '154 application recites "providing to the patient at least one other anticancer therapy." No arguments have been provided about how this claim or any of the other pending claims of the '154 application renders obvious *each* of claims of the present applications. In addition, the Action does not provide any arguments as to how any of the claims in either the '590 application or the '521 application render obvious each of the claims of the present application. There is, therefore, no basis for these rejections, and Applicants respectfully request that they be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner wish to discuss this further, please contact the undersigned attorney at 512-536-3081.

Respectfully submitted,

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